GI Drugs Advisory Committee Meeting

NDA 22-554 Xifaxan (Rifaximin)

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CDER/FDA

February 23, 2010

Proposed Indication

- The maintenance of remission of hepatic encephalopathy (HE) in patients 18 years of age or older

- **Decreasing the risk** for episodes of overt hepatic encephalopathy (HE) in patients 18 years of age or older

Issues

- Single pivotal phase 3 trial to provide substantial evidence of efficacy
- Adequacy of the primary endpoint definition and assessment methodology to evaluate hepatic encephalopathy
- Safety of rifaximin at the proposed dose and duration in patients with hepatic impairment

Definition of Substantial Evidence

Section 505(d) of the Act

"Evidence consisting of **adequate and well-controlled investigations**, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, **on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have** under the conditions of use prescribed, recommended, or suggested in the **labeling** or proposed **labeling** thereof"

FDAMA 1997
Amendment 505(d)

- Made clear that may consider data from **one adequate and well controlled investigation and confirmatory evidence** to constitute substantial evidence, if the FDA determines the data and evidence are sufficient to establish effectiveness
- If a single adequate and well-controlled study, the submitted study is held to a **higher standard**

Requirements for a Single Trial to be Sufficient

- Generally limited to situations where an adequate and well-controlled trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome AND
- A second adequate and well-controlled trial would be practically or ethically impossible

Limitations of Reliance on a Single Trial for Substantial Evidence

- Any trial may be subject to unanticipated, undetected, systematic biases
- Any trial may have a positive finding due to chance alone - a false positive finding
- Independent results help minimize an wrong conclusion that a drug is effective

Questions

1. How should remission be defined in overt episodic HE? Should patients with a Conn score of 1 be considered to be in remission?

2. For future clinical trials, what clinically meaningful endpoints should be evaluated and how should they be measured for:
   - decreasing the risk of episodes of overt HE
   - treatment of overt HE

3. Do the clinical data included in the rifaximin application provide substantial evidence of efficacy?

Questions

4. Has the safety of rifaximin at the proposed dose and duration been adequately assessed?

5. Is the safety of rifaximin at the proposed dose and duration acceptable?

6. Does the risk benefit profile support approval of rifaximin for decreasing the risk for episodes of overt HE?

NDA 22-554 Xifaxan (rifaximin) Advisory Committee Meeting

February 23, 2010

Lara Dimick, MD, FACS
Division of Gastroenterology Products

Rifaximin

Proposed indication: “maintenance of remission from Hepatic Encephalopathy in patients ≥ 18 years of age”

Dosage regimen: one 550 mg tablet twice daily (for chronic use)

Risk Factors and Concurrent Causes of Encephalopathy

- Electrolyte imbalance (Hyponatremia, Hypokalemia, Mn and Zn deficiency)
- Thyroid dysfunction
- Hypoglycemia
- Hypoxia, Hypercapnia
- Drug intoxication
- Dehydration
- Acidosis, Alkalosis
- Sepsis, fever
- Uremia, Azotemia
- Hypotension/hypovolemia
- Excessive protein intake
- Anemia (GI bleed, chronic)

Current Treatment Options for HE

Drug name	Drug class	Indication
Lactulose	Poorly absorbed disaccharide	-Decrease blood ammonia concentration -Prevention and Treatment of portal-systemic encephalopathy
Metronidazole	Antibiotic	Not approved for HE
Neomycin	Aminoglycoside antibiotic	Adjuvant therapy in hepatic coma
Vancomycin	Aminoglycoside antibiotic	Not approved for HE

Lactulose - NDA

- The NDA was approved in 1974 and was supported by multiple small studies.
- Most of these trials were for **treatment** of HE
- Some compared lactulose to neomycin and showed similar efficacy to neomycin.
- Some compared to placebo (sorbitol) and efficacy was mixed

Neomycin NDA

- Originally approved in 1965
- Indication: adjunct in management in hepatic coma by reducing ammonia forming bacteria in the intestine
- Limited data, small older trials

Cochrane Review

- "Nonabsorbable disaccharides for hepatic encephalopathy (Review)" 2004
- Summarized
  - Lactulose and lactitol
  - Antibiotics
- Methodology
  - Randomized
  - Acute, chronic, or minimal HE
  - **Treatment**
- Trial Quality Assessed
  - High quality = Adequate concealment of allocation AND adequate blinding

Cochrane Review

- "Non-absorbable disaccharides for hepatic encephalopathy systematic review of randomized trials"
  - British Medical Journal March 30, 2004
  - Als-Nielsen, B., Gluud, LL., Gluud C.
- Authors' Comments
  - Lactulose is a standard treatment for HE
    - Despite no benefit demonstrated in placebo comparisons
    - Based on 2 trials = comparisons to neomycin
      - "Equally Effective"
  - Flaws in this evidence trail
    - Little evidence supporting neomycin efficacy
      - Single placebo controlled trial (did not show benefit)
      - Single trial comparing Neomycin + Lactulose vs. Placebo
    - No significant difference does NOT mean "Equally Effective"

Lactulose vs. Non-neomycin Antibiotics
Cochrane Review

- None of the trials designed to demonstrate non-inferiority
- "Lack of statistical significance" does NOT equal non-inferiority
- "It seems that the research was continuously building up on both insufficient evidence and inadequate methods."

(Als-Nielsen, Gluud, Gluud; BMJ (2004))

Authors' Comments re: Antibiotics
Cochrane Review

- Placebo controlled trials of antibiotics don't establish efficacy of antibiotics
- Their meta-analysis indicated antibiotics are statistically superior to non-absorbable disaccharides
- They asked does statistically significant difference = clinically important difference?
- Concerned that potential risks (microbial resistance and adverse events) could outweigh the available evidence of efficacy
- Conclusion = insufficient evidence to recommend antibiotics for HE

(Als-Nielsen, Gluud, Gluud; BMJ (2004))

Lactulose vs. Placebo
Cochrane Review

10 trials (280 patients)

- 2 = High Quality (44 patients)
  - No significant effect
- 8 = Low Quality
  - A significant beneficial effect observed
  - The event rate in the control groups was significantly associated with whether the trial was high or low quality
    - » High = 38% event rate in the control arm
    - » Low = 78% event rate in the control arm

(Als-Nielsen, Gluud, Gluud; BMJ (2004))

Lactulose vs. Antibiotic
Cochrane Review

- 12 trials (698 patients)
  - 5 = High Quality (413 patients)
    - 3 Neomycin studies (270 patients)
    - 2 Rifaximin studies (143 patients)
  - 7 = Low Quality (285 patients)
    - 5 Rifaximin studies (210 patients)
- Pooled trials, High+Low
  - Significantly higher risk of no improvement with lactulose (1.24; 95% CI 1.02 to 1.50)

(Als-Nielsen, Gluud, Gluud; BMJ (2004))

Rifaximin vs. Lactulose
Cochrane Review Studies

- High Quality = 2 studies
- Mas, A, et. al (J. Hepatology 2003; 38(1):51-8)
  - N=103
  - Grade I-III acute HE
  - Changes in PSE index from baseline
    - 5 components = mental status, asterixis, time to do NCT, EEG abnormalities, blood NH3
  - Designed 80% power; Assume 80% success in lactulose and 95% success rifaximin

Rifaximin vs. Lactulose
Cochrane Review Studies

- Conclusions Mas, A, et. al (J. Hepatology 2003; 38(1):51-8)
  - No adjustment for multiplicity
  - Authors report rifaximin and lactulose demonstrate similar efficacy based on global assessment of efficacy

Issues

- Population definition
- Efficacy evaluation
  - Primary endpoint
  - Secondary endpoints
- Safety
  - Infection
  - Anaphylaxis
  - ? Hepatotoxicity

Current Submission

- Phase 3 Clinical Trials
  - RFHE3001 - Randomized, Placebo Controlled, Double blind (only pivotal trial)
  - RFHE3002 – Open label, Treatment extension
- Other Clinical Trials
  - Clinical Trials in HE Treatment
  - Clinical Trials for Other Indications
- Literature References

RFHE3001

Phase 3 - Efficacy and Safety Trial

Randomized, Double-Blind, Placebo Controlled, Two-arm, Multi-center

Entry Criteria

- Patients who had ≥ 2 episodes of overt HE associated with chronic liver disease (e.g., cirrhosis or portal hypertension) with a documented severity equivalent to Conn score ≥ 2 within 6 months prior to screening
- At enrollment the patients could have Conn scores of 0 or 1
- At least 1 of the prior episodes must have been verifiable from medical records

Entry Criteria

Hepatic encephalopathy episodes primarily attributed to GI hemorrhage requiring ≥ 2 units of blood by transfusion, medications (e.g., narcotics, tranquilizers, sedatives), renal failure requiring dialysis, or CNS insult such as a subdural hematoma were not counted as a prior, qualifying episode of HE

Conn Score - baseline

- 200 patients had Conn score of 0 at entry
  - 93 rifaximin
  - 107 placebo
- 99 had Conn score of 1 at entry
  - 47 rifaximin
  - 52 placebo

Indication

- **Maintenance of remission** from episodes of overt HE
- **Decreasing risk** of developing episodes of overt HE

Child Class – Baseline
RFHE3001

Class	Rifaximin N= 140	Placebo N = 159
Class A	46 (32.9%)	56 (35.2%)
Class B	65 (46.4%)	72 (45.3%)
Class C	17 (12.1%)	14 (8.8%)
Missing	12 (8.6%)	17 (10.7%)

MELD Score – Baseline
RFHE3001

MELD Score	Rifaximin N = 140	Placebo N = 159
≤ 10	34 (24.3%)	48 (30.2%)
11 - 18	94 (67.1%)	96 (60.4%)
≥ 19 ≤ 25	12 (8.6%)	14 (8.8%)
Missing	0	1 (0.6%)

Neurological Evaluation of Inclusion Criteria And Primary Endpoint Assessment

Ranjit Mani, MD

Conn Score (West Haven Criteria)

Conn score 0	No personality or behavioral abnormality detected
Conn score 1	Trivial lack of awareness, euphoria or anxiety; shortened attention span; impairment of addition or subtraction
Conn score 2	Lethargy; disorientation for time; obvious personality change; inappropriate behavior
Conn score 3	Somnolence to semi-stupor, responsive to stimuli; confused; gross disorientation; bizarre behavior
Conn score 4	Coma; unable to test mental state

Conn/West Haven Grading System

- Terms used for defining each grade
  - Imprecise
  - Dependent on clinician judgment
- Not sensitive for differentiating milder severities of HE

Inclusion Criteria

Key Inclusion Criteria

- Conn score (grade) of 0 or 1, indicating patient in remission from HE
- Two or more episodes of HE of Conn score ≥ 2 within 6 months prior to study
  - Episode defined as Conn score rising from 0 or 1 to ≥ 2, returning to a score of 0 or 1
  - At least one episode must have been confirmed by reviewing medical records from a treating physician, clinic, or hospital; other episodes could be based on caregiver description

Key Inclusion Criteria
QUESTION

- **In light of the study procedures, how reliably were prior HE episodes……**
  - **Identified?**
  - **Scored for Severity?**

Primary Endpoint

Primary Endpoint
Time to first breakthrough overt HE episode

- Defined as an increase of Conn score to Grade ≥ 2
- OR an increase in Conn score by 1 PLUS an increase in Asterixis score by 1
  - for subjects with Baseline Conn score 0

Primary Efficacy Parameter

Time to the first breakthrough episode of overt hepatic encephalopathy

Conn Score and Asterixis Grade determined by

- **Direct** assessment at study site visits OR
- **Indirect** assessment
  - Medical records
  - Hospital or emergency room physicians
  - Caregivers
  - Other sources

HESA

- Hepatic Encephalopathy Scoring Algorithm
  - Proposed as structured means of assigning Conn scores
  - Limited published experience
  - Validity uncertain
- Used in Study RFHE3001 as guide to Conn score assignment during direct assessment at study visits

HESA

- The HESA score was not recorded in Case Report Forms
- The manner in, and extent to, which the HESA was actually used to assign Conn scores is unclear

Conn Score Assignment

- The manner in which Conn scores were assigned based on indirect patient assessment is unclear

FDA Analysis of Primary Efficacy Parameter

Means of Diagnosing Breakthrough Overt HE from CRF - RFHE3001

Category	Placebo N = 70	Rifaximin N = 30	Totals N = 100
Direct (at site)	30 (42.9%)	8 (27.7%)	38 (38.0%)
Indirect hospitalized	19 (27.1%)	12 (40.0%)	34 (34.0%)
Indirect other	21 (30.0%)	10 (33.3%)	28 (28%)

Applicant Analysis of Primary Efficacy Parameter

Means of Diagnosing Breakthrough Overt HE
Additional Data from Applicant (N=4)

Category	Placebo N = 73	Rifaximin N = 31	Totals N = 104
Investigator	32 (44%)	11 (35%)	43 (41%)
ER/Hospital	26 (36%)	13 (42%)	39 (38%)
Caregiver reported	15 (21%)	7 (23%)	22 (21%)

Primary Efficacy Parameter
QUESTION

How reliably were breakthrough episodes of overt hepatic encephalopathy diagnosed during this study?

Concurrent Lactulose

Lara Dimick, MD, FACS

Concurrent Lactulose

- 273/299 ITT subjects on concomitant lactulose throughout treatment period
  - Rifaximin = 128 (91%)
  - Placebo = 145 (91%)
- Lactulose use balanced across study arms in this 273 patient subset

Concurrent Lactulose Usage

RFHE3001 was an add-on study

Rifaximin + Lactulose

vs.

Placebo + Lactulose

Primary Endpoint

Time to First Breakthrough Overt HE Event

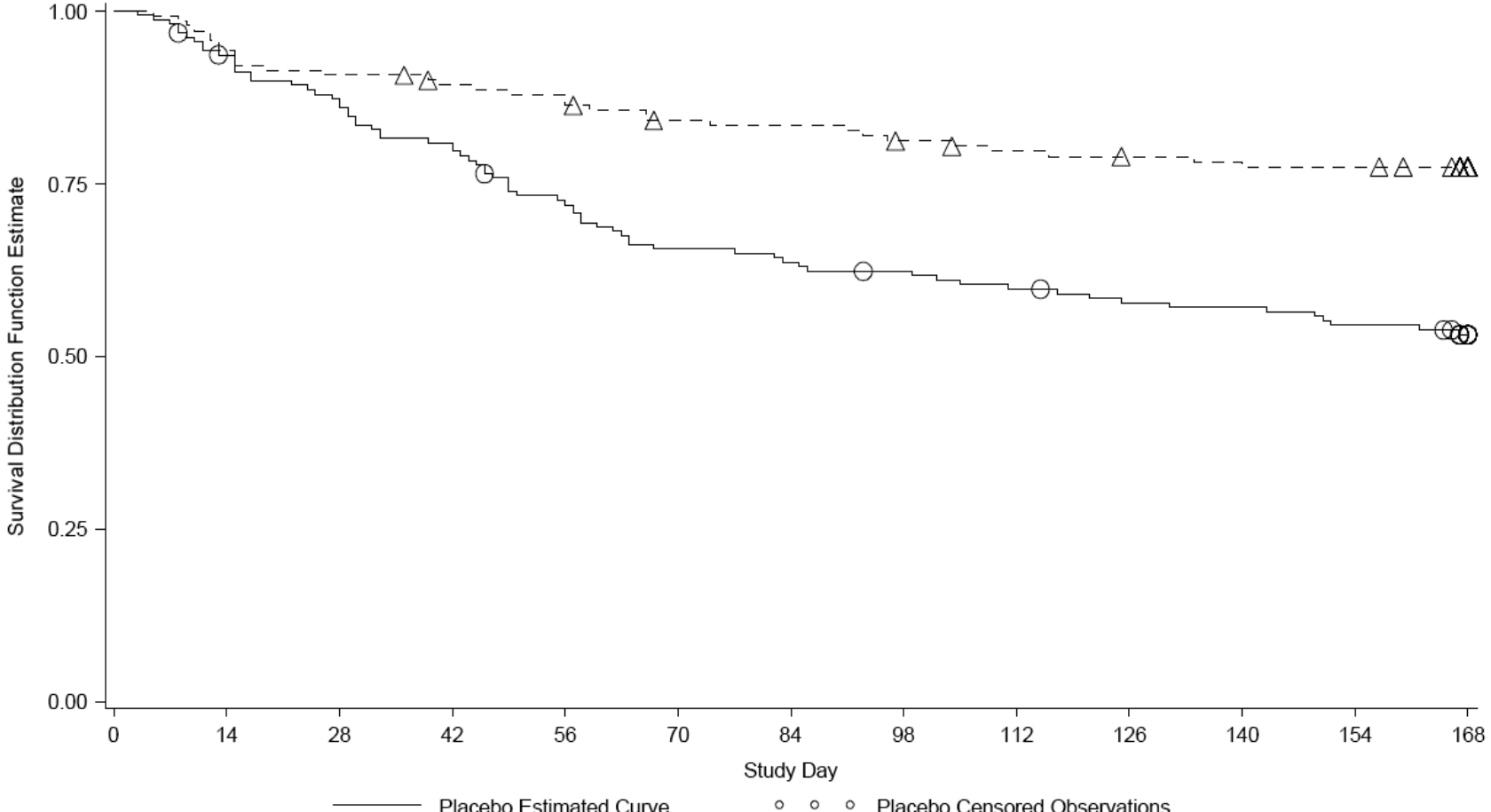
- Defined as an increase of Conn score to Grade ≥ 2
- OR an increase in Conn score by 1 **PLUS** an increase in Asterixis score by 1
  - for subjects with Baseline Conn score 0

Primary Endpoint Results

- Breakthrough HE events reported in
  - 31/140 Rifaximin
  - 73/159 Placebo
- Hazard ratio = 0.421, $p < 0.0001$,
  95% CI = (0.276, 0.641)
- 57.9% reduction in the risk of experiencing breakthrough HE event

Primary Efficacy Analysis
Time to First Breakthrough Overt HE Episode

Hazard Ratio Point Estimate = 0.421; 95% C.I. (0.276, 0.641), p<0.0001



Secondary Endpoints

Key Secondary Endpoint Prespecified Hierarchy

1. Time to first HE-related hospitalization.
2. Time to any increase from baseline in Conn score
3. Time to any increase from baseline in Asterixis grade
4. Mean change from baseline in fatigue domain score on the Chronic Liver Disease Questionnaire (CLDQ) at end of treatment
5. Mean change from baseline in venous ammonia concentration at end of treatment

Key Secondary Endpoints

- Applicant designated these secondary endpoints most clinically important
- Applicant pre-specified the order of their analysis

Multiplicity Adjustment

- Gate-keeping strategy utilized for key secondary efficacy analyses
- p-values and confidence intervals for all other analyses are presented with NO adjustment for multiplicity
  - Nominal p-values and confidence intervals are consequently exploratory and cannot be used as a basis for efficacy claims

Key Secondary Endpoint #1

Time to first HE-related hospitalization

- HE related hospitalizations were reported for
  - **Rifaximin = 19/140 (13.6%)**
  - **Placebo = 36/159 (22.6%)**
- Hazard ratio 0.500, p = 0.0129, 95% CI (0.287 to 0.873)
- No protocol specified criteria for admission

Other Secondary Endpoints

- Time to increase in Conn score – **statistically significant**
- Time to increase in Asterixis grade **failed** to meet statistical significance, therefore **all following secondary endpoint p-values cannot be used for efficacy claims**
- Including p-values on venous ammonia and Critical Flicker Frequency

Safety
Adverse Events

Serious Adverse Events
Infections

	RCT Safety Pop. (N = 299)		Long Term Safety Pop. (N = 336)		
	Placebo N = 159	Rifaximin N = 140	New Rifaximin N = 196	Cont. Rifaximin N = 140	All Rifaximin N = 336
C. difficile colitis	0	2 (1%)	3 (2%)	2 (1%)	5 (2%)
Pneumonia	1 (1%)	4(3%)	7 (3.6%)	5 (3.6%)	12 (3.6%)
Lobar pneumonia	0	0	1 (1%)	3 (2%)	4 (1%)
All infections, infestation	9 (6%)	11 (8%)	28 (14%)	22 (16%)	50 (15%)

Clostridium difficile Colitis

- Two events of *C. difficile* colitis in RCT Population
- 3 events in *C. difficile* colitis in Long Term Population
- Post-marketing 5 reported cases
  - 1 death

Immunogenicity

- Arthralgia
  - Rifaximin 6%
  - Placebo 3%
- Pyrexia
  - Rifaximin 6%
  - Placebo 3%
- Pruritis or rash
  - Rifaximin 21%
  - Placebo 15%
- Anaphylaxis
  - None in Phase 3 trials
  - Post-marketing reports of exfoliative dermatitis, angioneurotic edema, anaphylaxis

Cardiovascular Risk Evaluation

- hERG study weak in vitro inhibition
- No thorough Q/T study performed
- No ECG's done in any phase 3 trials

Deaths by Child-Pugh Class
RFHE3001

Class	Rifaximin	Placebo
Class A	n=46 2(4.3%)	n=56 2(3.6%)
Class B	n=65 3(4.6%)	n=72 8(11.1%)
Class C	n=17 3(17.6%)	n=14 1(7.1%)

Deaths by Child-Pugh Class
RFHE3002

Class	Rifaximin rollover	Placebo crossover
Class A	n=36 3(8.3%)	n=32 4(12.5%)
Class B	n=37 8(21.6%)	n=31 6(19.4%)
Class C	n=7 3(42.%)	n=5 1(20.1%)

Data Collection

- Lack of follow up data on patients who discontinued
- **No** LFT's drawn from 2 days prior to discontinuation through 30 days after the discontinuation on
  - Rifaximin 23/52 (44%)
  - Placebo 30/93 (32%)

Evaluation of AE's for Similar Drugs in Class

- Rifamycins are a group of structurally similar complex macrocyclic antibiotics
- Rifampin AE's include hypersensitivity, anaphylactic reactions, acute renal failure and hepatitis
- *DILI occurs very rarely in non-cirrhotic patient population, in this drug class as immunotherapy*
- Small case report studies of hepatotoxicity in cirrhotic population with rifampin

Is Rifaximin Hepatotoxic?

- Drug class raises potential
- Animal toxicity studies don't address this issue
- Increased systemic exposures with increasing Child-Pugh Class documented
- Lack of LFT data on discontinued subjects
- ? Increased death rate in Child-Pugh Class C observed

Preclinical Data

- Inconsistent toxicity finding – liver and small intestine
- No preclinical data in hepatic failure models

Preclinical Data
AUC values

Animal toxicity studies don't provide assurance of safety for rifaximin use in cirrhotic patients

- Inadequate systemic exposures in animals
- Animal toxicity study AUC's 42 -127 ng·hr/ml
- Cirrhotic patient mean AUC 130 ng·hr/ml
  Range = 28 - 359 ng·hr/ml

Clinical Pharmacology

Insook Kim, PhD

PK of rifaximin in patients with hepatic impairment

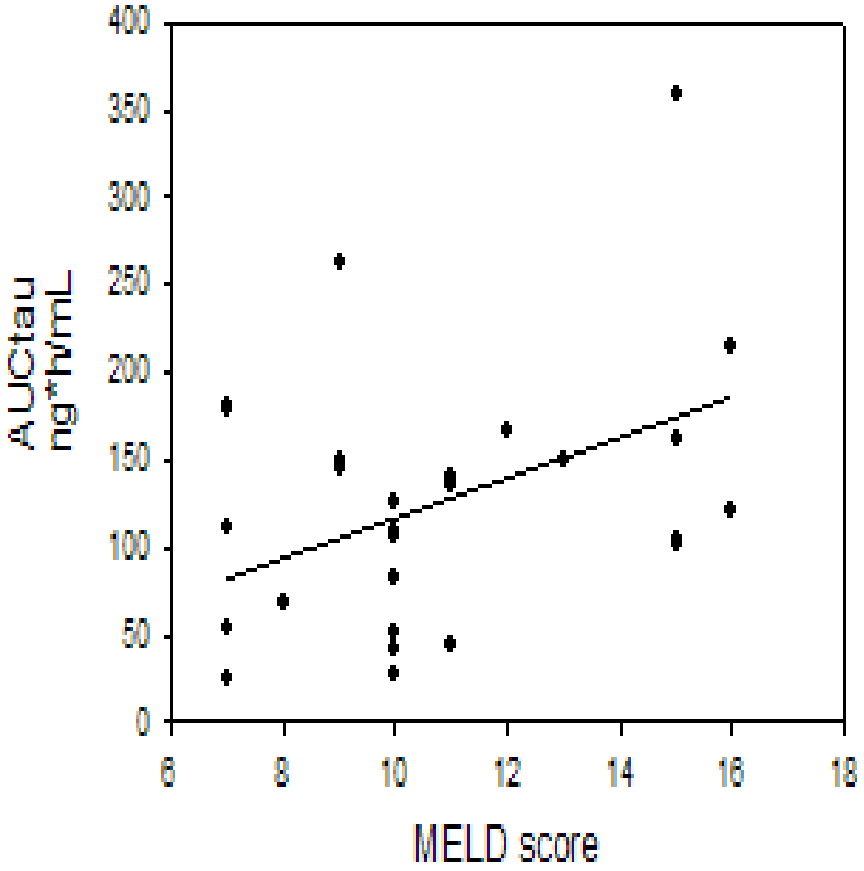
- The systemic exposure to rifaximin is markedly elevated in the proposed population, who by definition will have varying degrees of hepatic impairment
  - Current approved indication, traveler's diarrhea, is for population unlikely to have hepatic impairment
- The greater degree of hepatic impairment, the greater the increase in systemic exposure

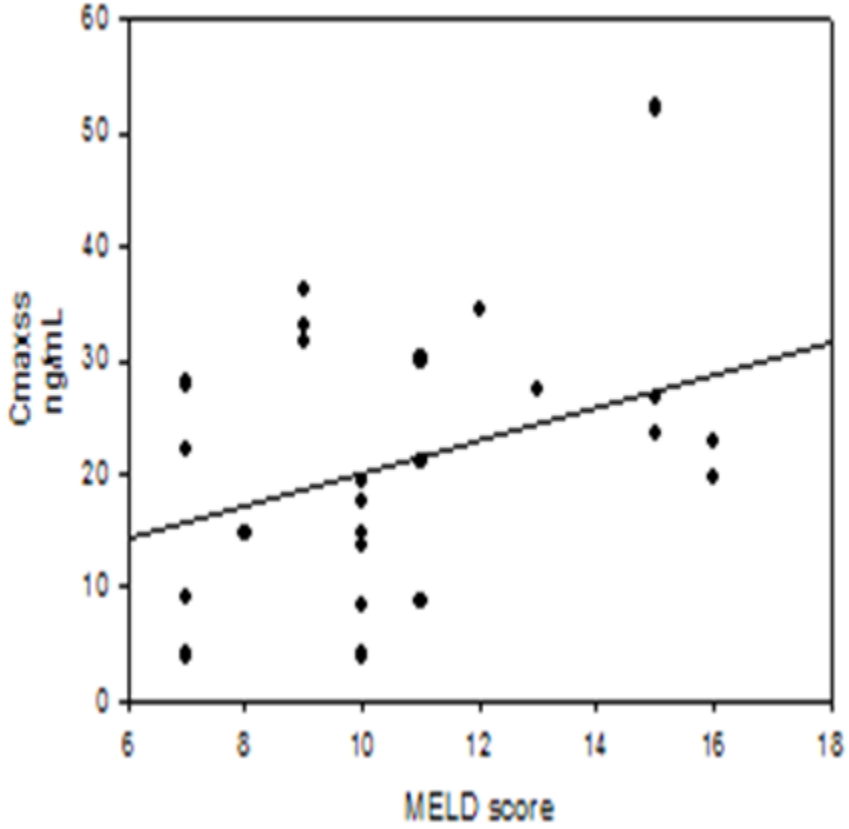
Rifaximin PK by Degree of Hepatic Impairment

	Healthy subjects (n=12)[1]	Child-Pugh A (n=18)[2]	Child-Pugh B (n=7)[2]	Child-Pugh C (n=4)[3]
AUCtau (ng·h/ml)	12.3 (4.76)	118 (67.8)	161 (101)	245.9 (119.6)
Cmax (ng/ml)	3.41 (1.62)	19.5 (11.4)	25.1 (12.6)	35.5 (12.5)
Tmax (h)	0.76 (0.5, 4)	1 (0.9,10)	1 (0.97, 1)	1 (0, 2)
CL/F (L/min)	863 (364)	122 (101)	70.6 (29.2)	--

Mean (SD) PK parameters at steady-state after 550 mg BID
1 Study RFPK1007
2 Study RFHE3002PK
3 Amendment on 1/26/10

Systemic exposure to rifaximin increases as MELD score increases





Extrinsic factors that may increase systemic exposure to rifaximin

- Food
  - A high fat meal increases AUC by 2-fold
- Concomitant medication
  - Efflux transporter inhibitor?
    - Rifaximin is a substrate of P-glycoprotein (P-gp) transporter
    - In presence of P-gp inhibitor e.g. verapamil, the efflux ratio of rifaximin was reduced in vitro
    - In vivo drug interaction was not evaluated

Summary

- Rifaximin is systemically available
- The degree of hepatic impairment has a significant effect on the level of systemic exposure to rifaximin
- Extrinsic factors may further increase the systemic exposure to rifaximin

Clinical Summary

Efficacy Summary

- Level of evidence – one controlled study
- Entry Criteria – definition of remission
- Assignment of Conn scores for breakthrough HE
- Concomitant Lactulose

Safety Summary

- Infections
  - *C. difficile* colitis
  - Other infections
- Anaphylaxis
- Hepatotoxicity in cirrhotics?
  - Drug class history
  - Lack of preclinical data
  - Increased systemic exposures with cirrhosis

Acknowledgements

- Kim, Insook, PhD, Clinical Pharmacology Reviewer
- Mani, Ranjit, MD, Consultant Neurology Reviewer, Division of Neurology Products
- Mehta, Niraj, PhD, Non-clinical Pharmacology Reviewer
- Purfield, Anne, PhD, Consultant Microbiology Reviewer, Division of Special Pathogens and Transplant Products
- Vali, Behrang, Statistical Reviewer

Questions?

Question 1 - Discussion

Study RFHE3001 enrolled a patient population with hepatic encephalopathy (HE). To be eligible patients had to have a history within the past 6 months prior to screening of ≥ 2 episodes of overt HE defined as Conn score ≥ 2. At enrollment the patients were required to have Conn scores of 0 or 1. At least 1 of the prior episodes must have been verifiable from medical records. Hepatic encephalopathy episodes primarily attributed to GI hemorrhage requiring ≥ 2 units of blood, medications (e.g., narcotics), renal failure requiring dialysis, or CNS insult were not counted as a prior, qualifying episode of HE.

Question 1 - Discussion

Two thirds of patients in the trial had a baseline Conn Score of 0 and 1/3 had a baseline Conn Score of 1. Ninety one percent of patients were taking lactulose.

- How should remission be defined in overt episodic HE? Should patients with a Conn score of 1 be considered to be in remission?

Question 2 - Discussion

For future clinical trials, what clinically meaningful endpoints should be evaluated (as primary and key secondary endpoints), and how should they be measured for:

- decreasing the risk of episodes of overt HE
- treatment of overt HE

Question 3 - Voting

Do the clinical data included in the rifaximin application provide substantial evidence of efficacy for an indication of maintenance of remission from HE (i.e., decreasing the risk for episodes of overt HE)?

In your response, please discuss your thinking regarding the following issues:

- Which clinical data, if any, provide substantial evidence of efficacy?
- What, if any, are the deficiencies in the clinical data that make the evidence less than substantial?

Question 4 - Voting

Has the safety of rifaximin at the proposed dose and duration been adequately assessed? In answering this question please discuss whether additional analyses or trials are needed.

Question 5 - Voting

Is the safety of rifaximin at the proposed dose and duration acceptable?

Question 6 - Voting

In light of the safety and efficacy data presented in this application, does the risk benefit profile support approval of rifaximin for an indication of maintenance of remission from HE (i.e., decreasing the risk for episodes of overt HE)?